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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,994	10/21/2003	Edgar B. Cahoon	BB1295USCNT	1315

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EXAMINER	
ZHENG, LI	
ART UNIT	**PAPER NUMBER**
1638	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,994	CAHOON ET AL.	
	Examiner	Art Unit	
	Li Zheng	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7282004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-11, 21, 23 and 24, SEQ ID NO: 16 and a plant cell, cancellation of claims 1-25, and submission of new claims 26-40 in the reply filed on 9/25/2006 are acknowledged. However, since applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In view of the cancellation of the previously pending claims and submission of new claims, all pending claims are drawn to the elected invention and are examined in this office action. As a result, claims 26-40 are pending and examined on the merits.

The requirement is deemed proper and is therefore made FINAL.

Priority

2. Support for the elected sequence of SEQ ID NO: 16 can be found in U.S. Provisional Application No. 60/127,111 filed on 3/31/1999 as SEQ ID NO: 12.

Specification

3. The status of the U.S. application recited on page 1, line 3 needs to be updated.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 26-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well-established utility.

The claims are drawn to an isolated polynucleotide encoding a polypeptide of SEQ ID NO: 16 or at least 80%/85%/90%/95% identity thereto, a vector comprising said polynucleotide, or a plant cell expressing said vector. The specification asserts that this polypeptide has diacylglycerol acyltransferase (DGAT) activity based on sequence comparisons with known or putative DGAT at pages 20-22. However, the sequence comparisons show that SEQ ID NO: 16 has as little as 30.9% sequence identity to a known DGAT fro *Mus musculus* and 65.9% sequence identity to a putative DGAT from *A. thaliana* (Table 6). In addition, the specification does not provide any additional information, such as an enzyme assay, to establish the utility of the claimed sequences. Sequence homology alone, however, is not sufficient to predict function of encoded sequences. See the teachings of Doerks et al. (June 1998, TIG 14, 6:248-250), where it states that computer analysis of genome sequences is flawed, and "overpredictions are

common because the highest scoring database protein does not necessarily share the same or even similar functions" (the last sentence of the first paragraph of page 248). Doerks et al. also teach homologs that do not have the same catalytic activity because active site residues are not conserved (page 248, the first sentence of the last paragraph). In addition, Smith et al. (November 1997, *Nature Biotechnology* 15:1222-1223) teach that "there are numerous cases in which proteins of very different functions are homologous " (page 1222, the first sentence of the last paragraph). Also, Brenner (April 1999, TIG 15, 4:132-133) discusses the problem of inferring function from homology, stating that "most homologs must have different molecular and cellular functions" (see the second full paragraph of the second column of page 132, for example). Furthermore, Borks et al. (Oct. 1996, TIG 12, 10:425-427) teach numerous problems with the sequence databases that can result in the misinterpretation of sequence data.

More specifically, identification of related sequences that will encode enzymes having a particular activity is particularly problematic in the enzymes involved in modifying fatty acid, and cannot be determined merely by similarity of DNA or amino acid sequences. Van de Loo et al. (July 1995, *PNAS USA* 92:6743-6747) teach that sequences encoding fatty acid hydroxylase activity are highly similar to other sequences that do not encode a hydroxylase, but instead encode a fatty acyl desaturase (see the abstract, at least). In fact, Broun et al. (Nov. 1998, *Science* 282:131-133) teach a change in only four amino acids will convert a desaturase gene to a hydroxylase gene (see the abstract, at least). Thus, if sequences are identified only by similarity to other

sequences that are known to encode DGAT, one cannot conclude that these other sequences also encode enzymes having DGAT activity.

Furthermore, the claims are not limited to the sequence encoding SEQ ID NO: 16, but are broadly drawn to sequences that have at least 80% identity thereto with no limitation that these sequences encode a DGAT. Therefore, no substantial or well-established utility has been provided for the claimed sequences.

A nucleotide sequence may be expressed in a transgenic host as contemplated by the applicants (page 23-27). However, such utilities are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Because a substantial and specific utility of the polynucleotide sequences is not established , a host cells expressing said polynucleotide sequences also lacks substantial and specific utilities. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleotide sequence such that another non-asserted utility would be well established for the compounds.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 26-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A review of the full content of the specification indicates that nucleotide sequences encoding polypeptides that are at least 80%/85%/90%/95% identical to SEQ ID NO: 16, are essential to the operation of the claimed invention.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that a written description of an invention "requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." (See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)). The court also concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. Further, the court held that to adequately describe a claimed genus, Patent Owner must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." Id.

A review of the language of claims indicates that claims are broadly drawn to transgenic plant comprising, or method requiring as starting material, a genus of

nucleotide sequences encoding polypeptides that are at least 80%/85%/90%/95% identical to SEQ ID NO: 16. However, neither the specification nor the prior art discloses any nucleotide sequence encoding a polypeptide that is at least 80%/90%/95%/98% identical to SEQ ID NO: 16 and also retains its functional activity, except for SEQ ID NO: 15. Since the activity of SEQ ID NO: 16 is not known, it is not known how to correlate other sequences to the activity of SEQ ID NO: 16, if any. Even if SEQ ID NO: 16 has DGAT activity as it is claimed in the specification, there is no conserved protein sequence described by either the specification or the prior art to correlated the conserved structure of DGAT to its enzyme activity. Therefore, given the breadth of the claims and the lack of further guidance, a person skilled in the art would conclude that applicant is not in possession of the claimed invention.

6. Claims 26-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Even if the biological function of SEQ ID NO:16 was known and enable, polypeptides that are at least 80%/85%/90%/95% identical to SEQ ID NO:16 would still not be enabled.

The specification teaches constructions of cDNA libraries from Arabidopsis, corn, rice, soybean and wheat tissues and identification of cDNA clones encoding putative

DGAT by BLAST search (pages 18-21). A soybean gene of SEQ ID NO: 15 encoding a polypeptide of SEQ ID NO: 16 that represents a putative full length DGAT enzyme, as determined by sequence homology, is also identified (Table 6). Expression of cloned putative DGAT genes in a monocot plant, dicot plant or microbial host is also contemplated (pages 23-27).

However, nucleotide sequences of the instant claims encompass any sequence that encodes a polypeptide that is at least 80%/85%90%/95% identical to SEQ ID NO: 16. The specification does not teach any function for SEQ ID NO: 16 other than potentially having DGAT activity according to sequence homology to known DGAT. Further, the specification fails to provide guidance in terms of how to make modifications to the SEQ ID NO: 16 to generate the claimed genus of sequences that retain its claimed DGAT activity. As discussed above, although the specification provides a consensus sequence through the alignment of several known/putative DGAT genes, they are obtained only by the sequence alignment without any experimental verification. There is no indication about the function importance of these motifs. Falcon-Perez JM et al. (1999, *J Biol Chem.* 274:23584-90) teach that when twenty-two single amino acid substitutions or deletions were introduced into the nucleotide binding domains, the proposed regulatory domain, and the fourth cytoplasmic loop of the yeast cadmium factor (Ycf1p) vacuolar protein by site-directed mutagenesis, two conserved amino acid residues, Glu (709) and Asp (821), were found to be unnecessary for Ycf1p biogenesis and function. The instant specification fails to provide guidance for which amino acids of SEQ ID NO: 14 can be altered, the type of alteration, and which amino

acids must not be changed, to maintain DGAT activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

Making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al. (1988, Mol. Cell. Biol. 8:1247-1252) teach that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins would have at least 95% identity to the original protein.

Guo et al. (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing claimed nucleic acid sequences or proteins would require undue experimentation.

In addition, De Luca (teaches that modifying plant biosynthetic pathways by transforming plants with genes encoding enzymes involved in said pathway is highly unpredictable (see the paragraph bridging the columns on the page 225N, for example), and that "on many occasions desired goals have been impossible to achieve" (see the last paragraph on page 228N). Therefore, both modifications of the DGAT gene encoding SEQ ID NO: 16 and plant lipid compositions by transforming a plant with said gene are highly unpredictable.

Given claim breadth, unpredictability of the art, and lack of working example and guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding a polypeptide having at least 80%/85%90%/95% identity with the polypeptide of SEQ ID NO: 16. See *Genentech Inc. v. Novo Nordisk,* A/S (CA FC) 42 USPQ2d 1001 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Conclusion

Claims 26-40 are rejected.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Li Zheng whose telephone number is 571-272-8031. The examiner can normally be reached on Monday through Friday 9:00 AM - 6:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571-272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ELIZABETH MCELWAIN
PRIMARY EXAMINER